(a) administering to said subject a composition containing a detectably labeled binding ligand capable of binding to ICAM-1, said ligand being selected from the group consisting of an antibody and a fragment of an antibody, said fragment being capable of binding to ICAM-1, and

(b) detecting said binding ligand.

97. A method of diagnosing the presence and location of inflammation resulting from a response of the specific defense system in a mammalian subject suspected of having said inflammation which comprises:

(a) incubating a sample of tissue of said subject with a composition containing a detectably labeled binding ligand capable of identifying a cell which expresses ICAM-1, and

(b) detecting said binding ligand.

C3 cancel

98. A method of diagnosing the presence and location of a tumor cell which expresses a member of the LFA-1 family of molecules in a subject suspected of having such a cell, which comprises:

(a) administering to said subject a composition containing a detectably labeled binding ligand capable of binding to a member of the LFA-1 family of molecules, said ligand being selected from the group consisting of ICAM-1 and a functional derivative of ICAM-1, and

(b) detecting said binding ligand.--

Remarks

Reexamination and reconsideration of this application are respectfully requested. In this Amendment, claims 84-86 have been canceled, claims 87-97 have been added, and claims 73 and 81 have been amended. Therefore, after this Amendment has been entered, claims 71-85 and 87-97 will be pending in this application.

Applicants note that the restriction requirement issued in the Office Action mailed on August 7, 1996, (Paper No. 3) has been withdrawn. Therefore, submitted herewith are claims directed to the previously non-elected inventions. In light of the withdrawal of the restriction requirement, Applicants respectfully request that these added claims be examined on the merits.

The Examiner also required the Applicant to verify and update the status of priority applications enumerated on page 1 of the specification. (Paper No. 6 at 2.) Applicants have appropriately amended the description of the priority applications, which was added to this application in an amendment filed on June 7, 1995, to update the status of parent Aplication No. 08/186,456 as United States Patent 5,612,216. The status of the remaining priority applications is correct as indicated in the amendment filed June 7, 1995.

The Examiner rejected claims 71-86 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. The Examiner presented several distinct grounds for this rejection. Applicants will address each ground in turn.

The Examiner noted that "[t]he term 'ICAM-1' when read in light of the specification has been interpreted as being limited to full-length, transmembrane human intercellular adhesion molecule-1, e.g., residues 1-505 as described in Fig. 8." (Paper No. 6 at 2.) However, the specification and priority applications characterize ICAM-1 in ways other than the sequence depicted in Figure 8. For example, ICAM-1 is characterized by molecular weight, domain structure, and functional properties in addition to a particular amino acid sequence. Thus, the term "ICAM-1," when read in light of the specification, refers to an intercellular adhesion molecule exhibiting identifying characteristics for ICAM-1 as described in the specification.

The Examiner also indicated that "[i]n claims 70 and 80 it is unclear what the scope of the term 'natural contaminant' is. Is this limited to cellular components found in human cells which express ICAM-1? Does this term encompass contaminants from prokaryotic or eukaryotic cells which have been engineered to express ICAM-1?" (Paper No. 6 at 3.)

Applicants note that the term "substantially free of natural contaminants" is defined on page 41 of the specification, in the context of the ICAM-1 molecule, as "[p]reparations which contain [ICAM-1 that] are substantially free of materials with which these products are normally and naturally found." (Specification at 41, lines 18-22.) Thus, the claimed preparation may contain contaminants, e.g., other proteins, with which ICAM-1 is not normally associated in nature. For example, if the presently claimed ICAM-1 preparation is made using recombinant expression methods, the presence of proteins derived from a heterologous host would not necessarily represent a "natural contaminant." Since one of ordinary skill in the art would be able to readily determine whether a particular component in the preparation is a natural contaminant, applicants submit this language is sufficiently definite to satisfy the requirements of 35 U.S.C. § 112, second paragraph.

The Examiner also alleged that "[i]n claims 73 and 81 it is unclear what the scope of the term 'bind lymphocytes' [or] 'lymphocyte binding' is. (Paper No. 6 at 3.) Applicants have appropriately amended these claims to refer to a specific binding to lymphocytes. Support for this amendment can be found, *inter alia*, at page 88, lines 14 to page 89, line 17, of the specification.[1] The sepcification and priority documents also provide one of ordinary skill in the art with an assay to determine whether the binding to lymphocytes is specific. In light of these

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[1]Analogous disclosure can be found in priority Application No. 07/045,963, filed May 4, 1987, at page 64, line 9 to page 65, line 20.

amendments and remarks, Applicants contend that their invention as instantly claimed in terms of specifically binding lymphocytes fully satisfies section 112, second paragraph.

The Examiner also alleged that claims 71, 80, 81 and 84-86 are unclear in what the scope of the terms "biological activity" or "biologically active" are. (Paper No. 6 at 3.) However, the specification provides significant information regarding the biological activity of ICAM-1. For example, the specification indicates that ICAM-1 can be used to inhibit inflammation, to bind LFA-1, to bind rhinovirus, to obtain antibodies capable of inhibiting inflammation, to obtain antibodies capable of inhibiting binding to LFA-1 or rhinovirus, and for various other diagnostic or therapeutic uses. In light of this detailed discussion of the biological activities of ICAM-1, it would be clear to one of ordinary skill in the art that the terms "biological activity" or "biologically active" encompass any one of the various ICAM-1 functional activities. Since these functional activities can be assayed based on the teachings in the specification, Applicants submit these terms are not indefinite. Merely because a term is broad does not render it indefinite. *In re Miller*, 169 U.S.P.Q. 597, 600 (C.C.P.A. 1971).

The Examiner has also alleged that the term "about" in claims 75-78 is vague and indefinite. (Paper No. 6 at 4.) However, the term "about" can be sufficiently definite to comply with 35 U.S.C. § 112, second paragraph in certain circumstances. *Amgen v. Chugai Pharm. Co. Ltd.*, 18 U.S.P.Q. 2d 1016, 1031 (Fed. Cir. 1991). "A decision as to whether a claim is invalid under this provision requires a determination whether those skilled in the art would understand what is claimed." *Id.* at 1030. In the present case, "about" relates to the molecular weight of various ICAM-1 molecules. The molecular weight was determined by SDS-PAGE. One of ordinary skill in the art would understand that a molecular weight of a protein species as determined by SDS-PAGE would be approximate. For example, the diffuse bands shown in

Figure 5 provide a basis for the degree of approximation encompassed by the pending claims. Thus, one of ordinary skill in the art would understand the limits of the term "about" in the context of the claimed invention. Therefore, Applicants submit that this term is sufficiently definite to satisfy the requirements of 35 U.S.C. § 112, second paragraph.

The Examiner also alleges that "[i]n claims 71-79 it is unclear what the term 'preparation' encompasses or excludes." (Paper No. 6 at 4.) The Examiner questions whether this term requires that the ICAM-1 product be produced by a particular preparative method or from a particular source. This term merely defines a composition comprising ICAM-1 in a purified or isolated form. The term "preparation" is not meant to define the ICAM-1 product in terms of a process by which it was produced. Thus, any composition containing purified or isolated ICAM-1, meeting all of the other recitations of the claims, regardless of how it was produced, falls within the scope of the pending claims.

The Examiner also alleges that claims 80-83 are unclear regarding the scope of the term "lipid membrane." Applicants submit the term "lipid membrane" would be apparent to one of ordinary skill in the art. For example, the term "membrane" is defined as a permeability barrier surrounding cells or organelles that consist of a bilayer of phospholipids and its associated proteins." *Concise Dictionary of Biomedicine and Molecular Biology 576* (1996). Thus, the term "lipid membrane" is meant to encompass any biological membrane including lipid bilayers formed of naturally occurring phospholipids, sphingolipids, or cholesterols as well as micelles or liposomes. Since the term "lipid membrane" has a specific definition to one of ordinary skill in the art, it does not render these claims indefinite. For these reasons, Applicants respectfully request that this ground for rejection be withdrawn.

The Examiner also rejected claims 71-86 under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make or use the invention. The Examiner provides three reasons to support this rejection. Each of these reasons will be addressed in turn.

First, the Examiner alleges that "[t]he specification only described ICAM-1 having the sequence set forth by Figure 8. No other amino acid sequences for native ICAM-1 products with different sequences are described." (Paper No. 6 at 6.) However, the specification adequately teaches one of ordinary skill in the art how to obtain ICAM-1 as instantly claimed and how to use ICAM-1 as instantly claimed. By way of example, the specification describes methods of obtaining ICAM-1 using antibody affinity on pages 20-22. This purification scheme is described in detail in Example 14. As described in the specification on page 66, ICAM-1 immunoprecipitated from different sources have different molecular weights. Thus, different ICAM-1 proteins can be obtained depending upon the initial source of material from which the purified ICAM-1 preparation is derived. Moreover, ICAM-1 has a variety of utilities, which are disclosed beginning on page 39 of the specification. For example, in solubilized form, these ICAM-1's may be employed to inhibit inflammation, organ rejection, or graft rejection. These ICAM-1's can also be used to block the metastasis or proliferation of tumor cells. Specific details concerning the administration of ICAM-1 for these utilities can be found in the specification beginning at page 41. In light of this information, Applicants submit that providing detailed amino acid sequence information for ICAM-1 is not required in order to enable one of ordinary skill in the art to make and use the invention as presently claimed.

The Examiner also argues that "[t]he specification does not adequately describe which preparations of ICAM-1 retain particular biological properties such as the ability to bind LFA-1, lymphocytes or HRV." (Paper No. 6 at 6.) In contrast to the Examiner's assertion, Applicants have provided significant information in the specification regarding the binding of ICAM-1 to particular ligands, such as LFA-1, LFA-1 expressing cell lines, lymphocytes, and HRV. (*See* Specification at 87-89 and 119 *et seq.*) Moreover, the ability of ICAM-1 to bind LFA-1, lymphocytes, or HRV represents an inherent property of the as-claimed ICAM-1 molecule(s). Thus, Applicants, by describing how to make and use ICAM-1, have adequately described their invention. Therefore, this reason does not support the Examiner's rejection.

The Examiner also alleges that the specification "only describes particular molecules on the surface of lymphocytes, such as LFA-1 or members of the LFA-1 family, which bind to ICAM-1." (Paper No. 6 at 6.) However, this reason does not relate to the ability of one of ordinary skill in the art to make or use ICAM-1. For example, one of ordinary skill in the art could make ICAM-1 and use ICAM-1 for various utilities without having identified other molecules on the surface of lymphocytes or other cells which may or may not bind ICAM-1. Therefore, this reason also does not support the Examiner's ground for rejection. For these reasons Applicants respectfully request that this rejection be withdrawn.

The Examiner rejected claims 80-83 under 35 U.S.C. § 112, first paragraph, for allegedly being enabled only for those forms of ICAM-1 products, lipid membranes, and methods of incorporation disclosed on page 85-87 of the specification. In making this rejection, the Examiner alleges that "use of different domains of ICAM-1 would impart different binding characteristics. Use of different types of lipids would result in different stabilities and

configurations of ICAM-1 within a membrane and result in a product with unpredictable stability, bioavailability and binding properties." (Paper No. 6 at 7.)

However, as discussed *supra*, one of ordinary skill in the art would be able to assay various lipid membranes for biologically active ICAM-1, based on teachings in the specification without undue experimentation. For example, the specification provides a detailed description of experimental procedures to incorporate ICAM-1 into artificial lipid membranes and to test ICAM-1 incorporated into lipid membranes for binding to LFA-1 expressing cells. (Specification at 86-89.) Moreover, ICAM-1 isolated as part of a native membrane would be expected to retain its native confirmation in the lipid bilayer thus preserving biological activity. For these reasons, this ground for rejection is improper and should be withdrawn.

The Examiner rejected claims 71-79, 84 and 86 under 35 U.S.C. §102(a) or (b) over Dustin *et al.*, *J. Immunol. 173:*245 (1986). In making this rejection, the Examiner alleged that the rejected claims "all embrace forms of ICAM-1 that are identical to those taught by Dustin et al." (Paper No. 6 at 8.) Applicants respectfully traverse this ground for rejection.

Applicants submit that the presently pending claims are fully supported by parent Application No. 07/045,963, filed May 4, 1987. Thus, the Dustin article does not qualify as prior art under 35 U.S.C. § 102(b), since it was published less than one year before Applicants' effective filing date. Applicants submitted a Declaration under 37 C.F.R. § 1.132 in parent Application No. 07/515,478 on May 19, 1993, to remove the Dustin article as prior art under 35 U.S.C. § 102(a). If a copy of this Declaration is not available to the Examiner, he is invited to contact the undersigned and an additional courtesy copy of the Declaration will be provided. Since the Dustin article does not qualify as prior art under either 35 U.S.C. § 102(a) or 35 U.S.C. § 102(b), Applicants respectfully request that this rejection be withdrawn.

The Examiner has rejected claims 71-79, 84, and 86 under 35 U.S.C. § 102(e) [hereinafter "Greve"] for allegedly being anticipated by Greve *et al.*, U.S. Patent 5,589,453 (priority to September 1, 1988). In making this rejection, the Examiner alleges that "[t]he cited patent, columns 4-7, teaches human rhinovirus receptor protein (now referred to as ICAM-1) prepared from HeLa cells with an Mr of about 95,000 Da and tryptic fragments of ICAM-1." (Paper No. 6 at 8-9.) Applicants respectfully traverse this ground for rejection.

Even if it is assumed, *arguendo*, that Greve is entitled to a section 102(e) date of September 1, 1988, this date is after the filing date of priority Application No. 07/045,963, filed May 4, 1987. Since all of the pending claims are entitled to priority under 35 U.S.C. § 120 from this priority application, Greve does not qualify as prior art under 35 U.S.C. § 102(e). Therefore, Applicants respectfully request that this ground for rejection be withdrawn.

The Examiner rejected claims 71-79 and 84-86 under 35 U.S.C. § 102(a) or (b) as being anticipated by, or alternatively under 35 U.S.C. § 103(a) as being unpatentable over Staunton *et al.*, *Cell 52:*925-933 (March 25, 1988), or Tomassini *et al.*, *Proc. Natl.Acad. Sci.(USA) 86:*4907-4911 (July 1989). Applicants respectfully traverse this ground for rejection.

Both the Staunton article and the Tomassini article were published after the filing date of parent Application No. 07/045,963. Therefore, for the reasons indicated *supra*, neither of these articles qualify as prior art under 35 U.S.C. §§ 102 and 103. Therefore, this ground for rejection should be withdrawn.

The Examiner also rejected claims 80-83 under 35 U.S.C. § 102(a) or (b) as being anticipated by, or alternatively under 35 U.S.C. §103(a) as being unpatentable over Staunton *et al.*, *Cell 52:*925-933 (1988) or Tomassini and further in view of "the admitted prior art on page 86 of the specification: Gay *et al.* or Brian *et al.*" (Paper No. 6 at 12.) Applicants respectfully traverse this grounds for rejection.

Applicants note that on page 86 of the specification contains a citation to Gay *et al.*, *J. Immunol. 136:*2026 (1986) and Brian *et al.*, *Proc.Natl. Acad. Sci.(USA) 81:*6159 (1984). However, the specification does not further characterize the legal status of these articles. Thus, there is no admission on page 86 of the specification that these articles represent prior art. As discussed *supra,* the Staunton and Tomassini articles do not qualify as prior art under 35 U.S.C. §§ 102 or 103. Moreover, the Gay and Brian articles are apparently relied upon only to show methods of preparation of vesicles or planar membranes and not to describe ICAM-1. Since Applicants' invention as instantly claimed relates to lipids containing purified or isolated ICAM-1, the Examiner has not established a *prima facie* case of unpatentability for anticipation or obviousness. Therefore, this ground for rejection should be withdrawn.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036. In the event an extension of time is necessary to prevent the abandonment of this application not accounted for herein, such an extension is specifically requested and the requisite fee should also be charged to our Deposit Account.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Robert C. Millonig
Attorney for Applicant
Registration No. 34,395

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1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

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